REMARKS

In the present Application, Claims 1-4, 11 and 22 have been amended, Claim 15 has been cancelled, and Claims 25-32 have been added. As such, Claims 1-14 and 21-32 are currently pending.

The Examiner's rejections are as follows:

I. Claims 1-2, 21, and 23-24 were rejected under 35 U.S.C. 102 as allegedly anticipated by Yan et al.;

II. Claims 3-13 and 15 were rejected under 35 U.S.C. 103(a) as allegedly obvious over Yan et al., in view of Ferguson et al., Herman et al., Bovenzi et al., Du et al., Paz et al., and Worm et al.; and

III. Claim 14 was rejected under 35 U.S.C. 103(a) as allegedly obvious over Yan et al., in view of Ferguson et al., Herman et al., Bovenzi et al., Du et al., Paz et al., Worm et al., and further in view of Huang.

Applicants submit that the arguments and amendments described below traverse the Examiner's rejections.

I. Novelty Rejection of Claims 1-2, 21, and 23-24

The Examiner rejected Claims 1-2, 21, and 23-24 as allegedly anticipated by Yan et al. As part of this rejection, the Examiner addressed the limitations of Claim 2 and asserted that "Yan further teaches genomic DNA was digested with MseI which is methylation sensitive and followed by amplification" (Office Action, page 3). Applicants respectfully disagree with the Examiner's characterization of this reference and submit that Yan et al. does not teach digesting genomic DNA with a methylation sensitive restriction enzyme. First, Applicants note that MseI is not a methylation sensitive restriction enzyme (See, e.g., NEB Catalog page for MseI at http://www.neb.com/nebecomm/products/productR0525.asp). The Yan et al. reference itself acknowledges that MseI reference does not cleave CpG islands. MseI was used in the Yan et al. reference to restrict the genomic DNA into <200 bp fragments such that linkers could be attached to the ends of generated fragments. Second, Yan et al. did employ a methylation sensitive restriction enzyme called BstU1 as part of their protocol (Yan et al., page 1433, 1st col.). However, the BstU1 was used to digest the recombinant fragments generated by ligating linkers to the MseI generated fragments. As such, BstU1 was used in Yan et al. to digest these

recombinant fragments, not genomic DNA (i.e., BstU1 was not applied to genomic DNA). As Claim 2 specifically recites that the genomic DNA is digested with the methylation sensitive restriction enzyme, this limitation is not taught by the Yan et al. reference.

To expedite prosecution, and without acquiescing to the Examiner's rejections, Applicants have amended Claim 1 with the limitations of Claim 2. As Claim 1 now recites "digesting said genomic DNA in said biological sample with a methylation-sensitive restriction enzyme," it is clear that Yan does not anticipate this amended Claim.

One additional amendment made to Claim 1 is the addition of step c) which recites the use of gene specific primers to amplify fragments of the promoters that were not cleaved by the methylation sensitive restriction enzyme, where the primers are configured to hybridize to the genomic DNA. It is noted that the primers in Yan et al. were not gene specific, but instead were a single pair of universal primers specific for the linkers. Moreover, the Yan et al. primers were configured to hybridize to the linkers, not configured to hybridize to the genomic DNA to amplify uncleaved regions. As such, this is an additional reason that Yan does not anticipate amended Claim 1.

Applicants also note that new Claim 31 has been added which recites that the digestion is "performed to completion.[1]" Support for this amendment can be found in the specification at, for example, page 73, lines 19-20. The Yan et al. reference does not indicate that the BstU1 digestion of the recombinant linker fragments was performed to completion. New Claims 25-28 were also added to recite particular embodiments related to, for example, quality control procedures to ensure digestion is performed to completion. Support for these claims can be found, for example, in Example 1.

II. Obviousness Rejection of Claims 3-13 and 15

The Examiner rejected Claims 3-13 and 15 under 35 U.S.C. 103(a) as allegedly obvious over Yan et al. in view of Ferguson et al., Herman et al., Bovenzi et al., Du et al., Paz et al., and Worm et al. The Examiner cites Yan et al. as teaching "hypermethlation of numerous nucleic acids," but admits that Yan et al. does not teach detecting methylation in any of the eight genes

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[1] Applicants note that digestion to "completion" is widely understood in the art to not mean that every single digestable molecule in the tube be cleaved, but instead that most of such molecules be cleaved such that any remaining uncleaved molecules are generally considered to be at undectable levels, unless extreme measuring techniques are used in an effort to detect such molecules.

recited in Claim 3, let alone all eight (Office Action, page 5). The Examiner then cites the remaining six references as each teaching one or a couple of the eight recited genes in Claim 8. The Examiner argues that it would have been obvious to modify the profiling method of Yan to include additional known methylated genes of Ferguson, Herman, Bovensi, Du, Paz, and Worm, and that the ordinary artisan would have been motivated to include any number of CpG islands on the array for deciphering epigenetic signatures of breast cancer. Applicants respectfully disagree with this rejection.

Applicants submit that the Examiner has not properly characterized the Yan reference and the Differential Methylation Hybridization method (DMH) described in this reference. In particular, Applicants note that one does not "select" particular genes to be located on the array in DMH. Instead, as shown in the Figure below from Huang et al., (Hum. Mol. Genet., 8:459-470, 1999), reference as the source of DMH in Yan et al., the CpG tags that are on the panel come from the tumorigenic cells (i.e., one is not deciding what to include or not include on the panel).

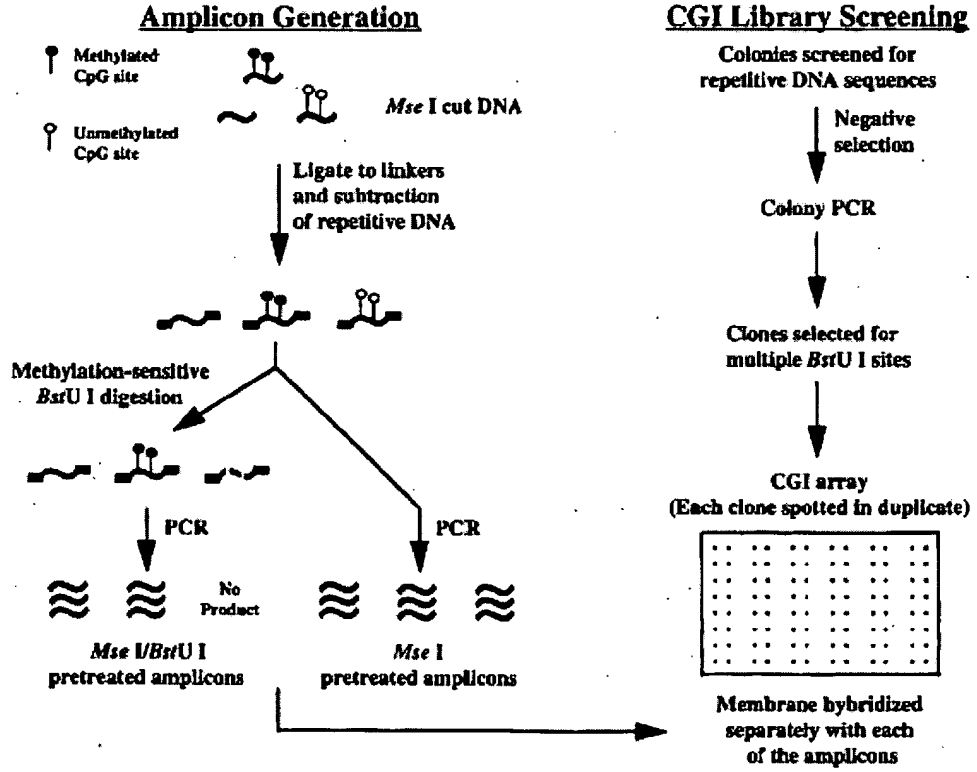

Figure 2. Schematic flowchart for differential methylation hybridization. A detailed description of each step is given in Materials and Methods. The diagram illustrates the preparation of amplicons used as hybridization probes and selection of CpG island genomic clones gridded on high-density arrays.

In light of how DMH operates, Applicants strongly disagree with the Examiner's assertion that one of skilled in the art would have been motivated to select any particular gene for the array, let

alone the eight recited in Claim 3. In light of lack of selection in the primary reference cited by the Examiner, Applicants submit that the Examiner's stated motivation fails and therefore no *prima facie* case of obviousness has been established.

Applicants note that the Examiner has also pointed to the Ferguson reference, page 44, column 2, as teaching a "panel." While the Examiner did not point to this section as part of the motivation to use multiple genes, Applicants wish to note the section in Ferguson cited by the Examiner also relies on the DMH assay, and specifically cites the Huang et al. reference. As such, for the same reasons Yan et al. does not provide a motivation to combine the references, the Ferguson et al. reference also fails to provide such a motivation.

In regards to the *particular* eight genes recited in Claim 3, Applicants submit that the Examiner has failed to allege a motivation for combining this *particular* set of eight genes. Applicants submit that none of the references cited by the Examiner provide a motivation for combining this particular set of genes. The Examiner has simply found references that may mention one or a number of the particular genes in Claim 3, but has failed to point to a motivation in these references (or in Yan et al.) why one of skill would assemble this *particular* combination. Such hindsight reconstruction is improper under Federal Circuit precedent *(see, In re Dembiczak*, 175 F.3d 994, 999, "Our case law makes clear that the best defense against the subtle but powerful attraction of a hind-sight based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references."). Applicants submit that no such motivation has been provided for the particular combination of genes recited in Claim 3. Applicants further submit that the Examiner will not be able to point to such a motivation to combine the references as the combination of genes recited in Claim 3 was *empirically* derived (see Example 1 of the specification).

The same lack of obviousness applies to new Claim 32, which recites detecting the same collection of eight genes as Claim 3, but in a "consisting of" format. The Examiner's arguments that one would put any number of genes on a panel is further diminished by this claim as there is no guidance or motivation in the cited references to include certain genes and exclude others.

From the above it is clear that the Examiner has not establish a *prima facie* case of obviousness for Claim 3, and claims dependent thereon. Nonetheless, in order to expedite the prosecution of the present application, without acquiescing to the Examiner's rejections, while reserving the right to pursue the original claims in the future, Applicants have amended Claim 3

to recite that the subject has "breast" cancer. Applicants submit that this amendment further highlights the lack of obviousness of the claims. In particular, two of the genes recited in Claim 3, p15 and DAPK, are not taught or taught away from, in the references cited by the Examiner. For example, the Examiner cited the Herman et al. reference as teaching methylation of p15 in cancer. The Herman reference indicates that such methylation is found in gliomas and leukemias, and "occurs only rarely and only with concomitant inactivation of p16" in breast cancer (see Herman et al. Abstract). Applicants submit that this reference teaches away from including p15 in a set of genes to screen from a *breast* cancer sample as rarely methylated (and inactivated) genes would appear to provide the opposite of a reliable diagnostic. Likewise, the Examiner cited the Paz et al. reference as teaching methylation of DAPK in cancer. The Paz et al. reference, however, describes only assaying for DAPK methylation in lung tumors, while breast tumors were assayed for a number of other genes not including DAPK. The Paz et al. reference also provides a teach away as the authors of this reference were testing breast tumor tissue and were assaying for DAPK, but failed to combine the DAPK assay with the breast tissue, making it clear that they did not realize their was any merit to testing breast tissue for DAPK. In light of the lack of teachings in these references, it is clear that amended Claim 3 is nonobvious.

Finally, Applicants note that dependent Claim 11, which recites that the biological sample is a blood sample (now amended to plasma), has not been addressed by the Examiner. Applicants submit that none of the references cited by the Examiner teach or suggest this limitation. Therefore Claim 11 should be allowed.

III. Obviousness rejection of Claim 14

The Examiner rejected Claim 14 under 35 U.S.C. 103(a) as allegedly obvious over Yan et al. in view of Ferguson et al., Herman et al., Bovenzi et al., Du et al., Paz et al., Worm et al.. and further in view of Huang (US Pat. 6,605,432). The Examiner repeats the obviousness rejection from above, and includes Huang as teaching the use of Hin6I. For the same reasons noted above, Claim 14 cannot be obvious (both before and after the amendment to Claim 3 adding the breast cancer limitation). The Huang patent fails to make up for the deficiencies of the cited references as it also describes the DMH assay. As such, no *prima facie* case of obviousness has been established for Claim 14. Moreover, the Huang patent fails to actually teach Hin6I as recited in Claim 14. As such, this rejection should be withdrawn.

IV. Supplemental IDS

A supplemental information disclosure statement is being filed with this communication. This supplemental information disclosure statement provides the following two references: 1) Singer-Sam et al., Nucleic Acids Research, 18(3):687 and 2) Singer-Sam et al., Molecular and Cellular Biology, Sept; 10(9):4987-4989. Applicants request that these references be made of record.

CONCLUSION

Should the Examiner believe that a telephone interview would aid in the prosecution of this application, the applicant encourages the Examiner to call the undersigned collect at (608) 218-6900.

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Jason R. Bond
Registration No. 45,439

MEDLEN & CARROLL, LLP
101 Howard Street, Suite 350
San Francisco, California 94105
608.218.6900